Effects of Platelet-Rich Plasma and Concentrated Growth Factor on Viability of Ultra-Diced Cartilage Grafts in a Rabbit Model

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Background: Although rhinoplastic surgery has progressed considerably in recent years, nasal dorsal irregularities still cause postoperative distress for both surgeons and patients.

Purpose: The aim of this study was to measure the association between two biologic graft adjuncts, platelet-rich plasma (PRP) and concentrated growth factor (CGF), and ultra-diced cartilage viability in an animal model.

Study Design, Setting, and Sample: This study was designed as a randomized in-vivo study using a rabbit model. Fourteen rabbits were utilized in this investigation. The ultra-diced cartilage was obtained from auricular cartilage.

Predictor Variable: The graft biologic adjunct is the predictor variable. There were three treatment groups: graft mixed with PRP or CGF or untreated (control). The grafts were placed in three separate pockets opened on the same rabbit. Grafts were harvested 3 months after insertion for analysis.

Main Outcome Variable(s): The primary outcome variable was histopathological and regenerative scores obtained from multiple histopathological parameters indicating the viability of the cartilage. Histopathological score parameters were chondrocyte loss, inflammation, fibrosis, cartilage fragmentation, and calcified area formations in the lacunae. Regenerative score parameters were peripheral cell proliferation in the cartilage tissue, vascularization in the connective tissue, proteoglycan increase in the matrix, and the amount of connective tissue.

Covariates: The variables were age, sex, and weight.

Analyses: Statistical analysis employed the analysis of variance test, with a significance level of $P < .05$.

Results: The sample was composed of 14 rabbits and 42 samples. The histopathologic scores were 11.93 ($\pm$2.49), 8.78 ($\pm$2.19), and 6.85 ($\pm$1.46) for the control, PRP, and CGF groups, respectively. A statistically significant difference was found in the PRP ($P < .0275$) and CGF ($P < .0001$) groups compared to the control group. The regenerative scores were 6.21 ($\pm$0.97), 8.85 ($\pm$1.70), and 12.07 ($\pm$1.26) for the control, PRP and CGF groups, respectively. A statistically significant difference was found in the PRP ($P < .0159$) and CGF ($P < .0001$) groups compared to the control group.

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Conflict of Interest Disclosures: None of the authors have any relevant financial relationship(s) with a commercial interest.

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Received February 5 2024

Accepted May 31 2024

0278-2391/24/00390-2

https://doi.org/10.1016/j.joms.2024.05.041

Conclusion and Relevance: This is the first study investigating the ultra-diced cartilage graft in an experimental animal model. Histopathological examination has shown that mixing ultra-diced cartilage with CGF or PRP increases viability by reducing the histopathological score and increasing the regenerative score.

J Oral Maxillofac Surg 82:1067-1075, 2024

The purpose of rhinoplasty is to give the nose a natural and symmetrical appearance. However, sharp-edged and irregular nasal bones and cartilages may develop after nasal hump resection. This may cause the nasal dorsum to appear uneven and cause an open roof deformity.[1] This irregularity usually occurs after the postoperative edema has subsided or may occur months or even years later.[2] Many solutions have been proposed for the elimination of dorsal irregularities.[3-5] However, autogenous cartilage is the ideal graft material for rhinoplasty because of its low graft rejection, low infection risk, and minimal graft visibility.[6]

Diced cartilage with a size of 0.5-1 mm was first introduced by Peer in 1943.[7] However, it was not until the 2000s that this graft gained popularity in rhinoplasty. In his 10-year study, Erol found that diced cartilage wrapped with oxidized regenerated cellulose (Surgicel) was suitable for strengthening the nasal dorsum and correcting dorsal irregularities.[8] But later Daniel and Calvert showed that wrapping of diced cartilage with oxidized regenerated cellulose reduced cartilage graft viability and suggested the use of deep temporal fascia for wrapping.[9] The most common problems in the use of diced cartilage grafts are the wrapping material to be used and cartilage resorption.[10] Studies so far have tried to increase the viability of cartilage grafts and achieve permanent and invisible cartilage grafts in the long term. There are studies in the literature suggesting the utilization of blood products to increase the viability of autogenous cartilages.[11,12]

The five main growth factors found in platelets and plasma are platelet-derived growth factor, fibroblast growth factor, transforming growth factor-ß, vascular endothelial growth factor, and insulin-like growth factor. It is known that platelet concentrates containing these factors increase tissue regeneration and healing.[13] Platelet-rich plasma (PRP) is a plasma fraction with a relatively higher concentration of platelets produced from autologous blood samples.[14] PRP has several different growth factors and cytokines that stimulate bone healing. Concentrated growth factor (CGF) defined by Sacco in 2006, is obtained by centrifugation of venous blood and takes the form of a gel. It is denser than PRP and richer in growth factors.[15,16] It has been used for different purposes in many surgical fields for about 30 years. It also increases the viability of cartilage grafts used in rhinoplasty.[17]

Ultra-diced cartilage, consisting of cartilage fragments smaller than 0.2 mm, was first described by Taş in 2021. In his study, Taş argued that ultra-diced cartilage was superior to diced cartilage in terms of graft visibility and structural skeletal requirements. The viability of the ultra-diced cartilage has been demonstrated histopathologically in only 1 patient undergoing revision.[18]

The purpose of this study is to histopathologically investigate the viability of cartilage grafts by mixing the ultra-diced cartilage with PRP, CGF, or leaving it bare, respectively. The authors hypothesize that the cellular viability of the graft as measured using histopathologic parameters will differ among the two biologic adjuncts and an untreated control group. Additionally, the specific aim of this study is to compare the viability of cartilage mixed with PRP and CGF.

Materials and Methods

STUDY DESING AND STUDY SAMPLE

In the study, 14 New Zealand rabbits, 12 weeks old, with an average of 3.5 kg, were used. All surgical procedures were performed in accordance with ethical principles and guidelines for experiments on animals. Ethical approval was obtained by Bezmialem Vakıf University Experimental Animals Local Ethics Committee. All animal care and surgical procedures are humanely done.

VARIABLES

The predictor variable was adjunct graft biologic and there were 3 groups, PRP, CGF, and untreated control. PRP and CGF were prepared with 20 cc of blood taken from rabbits. An ultra-diced cartilage graft was obtained from rabbit auricular cartilage. The ultra-diced cartilage was mixed with PRP, CGF, or left it bared (control). The grafts were placed in three separate pockets opened on the back of the same rabbit. Grafts were harvested 3 months after insertion for analysis.

The primary outcome variables were graft viability measured using histopathologic and regenerative scores. Histopathological score parameters were chondrocyte loss, inflammation, fibrosis, cartilage fragmentation, calcified area formations in the lacunae. Regenerative score parameters were peripheral cell

proliferation in the cartilage tissue, vascularization in the connective tissue, proteoglycan increase in the matrix and the amount of connective tissue. The evaluation parameters range from 0 to 4 (0 = 0%-1% absent, 1 = 1%-25% mild, 2 = 26%-50% moderate, 3 = 51%-75% moderate-severe, and 4 = 76%-100% severe) was determined. The histopathologic score was calculated by summing the scores of the histopathologic parameters after they were scored. Similarly, the regeneration score was calculated by summing the scores of the regenerative parameters after they were scored. Lower histopathologic scores suggested more viable tissues than higher scores. On the contrary, higher regenerative scores suggested more viable tissues than lower scores. The covariates for the study were age, sex, and weight.

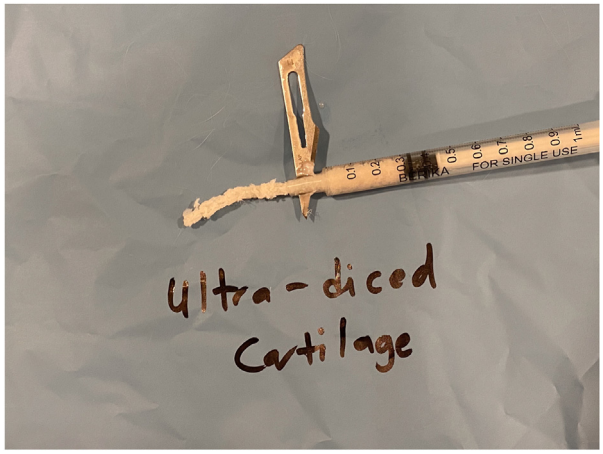

FIGURE 1. Ultra-diced cartilage graft.

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Data Collection Methods

SURGICAL PROCEDURE

Each rabbit was anesthetized by intramuscular injection of 35 mg/kg ketamine hydrochloride and 5 mg/kg xylazine hydrochloride. The ears of the animals were disinfected with povidone iodine. All surgical procedures were performed under aseptic conditions.

An incision was made in the right auricle of each rabbit. After passing the skin, subcutaneous tissue and perichondrium, the cartilage tissue was reached. A 5 × 4 cm cartilage graft was taken. The cartilage graft was divided into 2-3 mm pieces using a No. 11 scalpel. Two insulin syringes were prepared by stabbing through the narrow end with No.11 scalpel facing sharp edge toward the syringe chamber as described by Taş.[18] After filling the first insulin syringe with roughly diced cartilage pieces, the syringe was injected into the chamber of the second insulin syringe. During the transfer from 1 injector to the other, the roughly diced cartilage tissue was increasingly chopped each time. By repeating this several times, an ultra-diced cartilage graft resembling a cartilage paste was obtained (Fig 1).

For PRP, 10 cc of blood samples taken from rabbits were placed in blood tubes containing anticoagulant. To concentrate the platelets, it is necessary to use a double centrifugation technique. It was separated into 3 layers in the first centrifugation at 1600 rpm for 10 minutes. From top to bottom: platelet-poor plasma, platelets, and red blood cells. The upper and middle layers were then transferred to a new tube without anticoagulant. This tube was taken to a second centrifugation at 3500 rpm for 15 minutes. In this way, the platelets were concentrated at the base and two-thirds of the platelet-poor plasma above it was discarded. Thus, PRP was obtained with the remainder of the tube (Fig 2).[19] Then, approximately 1 cc of this PRP was taken into the injector. Ultra-diced cartilage was placed in the subcutaneous pocket after a 1.5 cm incision. The incision was closed tightly to prevent leakage. Then, 1 cc of PRP was injected into the subcutaneous pocket through the incision.

In addition, for CGF, another 10 cc of venous blood from rabbits was collected and placed in a sterile 10 ml blood tube without anticoagulant. This tube was then immediately centrifuged for 13 minutes in a special centrifuge (Medifuge; Silfradent Srl, Sofia, Italy). On this device a special program is used: 2700 rpm for 2 minutes, 2400 rpm for 4 minutes, 2700 rpm for 4 minutes, and 3000 rpm for 3 minutes. At the end of centrifugation, there were four fractions in the tube: (1) the uppermost serum layer (blood plasma without fibrinogen and coagulation factors); (2) a fibrin buffy coat (large and densely polymerized fibrin block); (3) a fluid layer containing growth factors, white blood cells, and stem cells; and (4) the lowest red blood cell layer (Fig 2). Fibrin buffy coat and liquid phase (second and third layers, respectively) were used in the experiments in this study. The red blood cell layer was separated from the fibrin block with a scissors. Afterward, this prepared CGF layer was sandwiched between two glasses to obtain CGFgel.[20] This gel layer containing CGF was divided into small pieces and mixed with the ultra-diced cartilage graft. The graft was inserted into the subcutaneous pocket that had been previously opened with bayonet forceps.

Three groups were assigned according to the type of graft to be used in 14 rabbits.

Group 1: Only ultra-diced cartilage grafts.

Group 2: Ultra-diced cartilage grafts mixed with PRP.

Group 3: Ultra-diced cartilage grafts mixed with CGF.

Three skin incisions approximately 1.5 cm long were opened in the paraspinal region of the rabbits and small subcutaneous pockets were created. Three

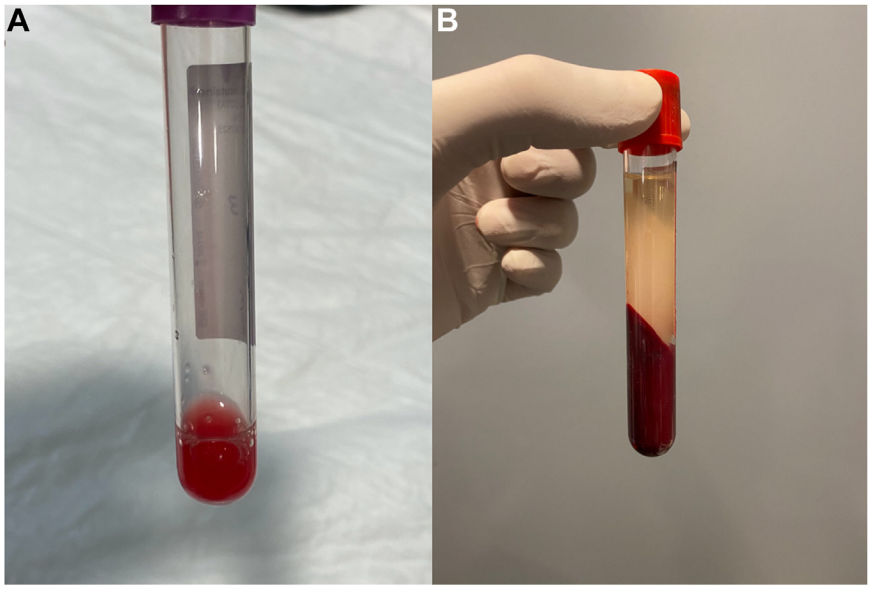

FIGURE 2. Tubes after centrifugation to obtain PRP (*A*) and CGF (*B*). CGF, concentrated growth factor; PRP, platelet-rich plasma.

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grafts were placed respectively into three separate subcutaneous pockets opened on the back of the same rabbit. The graft mixed with PRP was placed in the first pocket, the graft mixed with CGF was placed in the second pocket, and the control group was placed in the third pocket. The incisions were closed using 4/0 Vicryl sutures. No complications were observed in the recipient areas in the postoperative period. No instances of animal mortality or graft loss occurred during the study. Three months later, the implanted grafts were excised for histopathological evaluation (Fig 3). Rabbits were sacrificed with a high dose (150 mg/kg) of thiopental sodium.

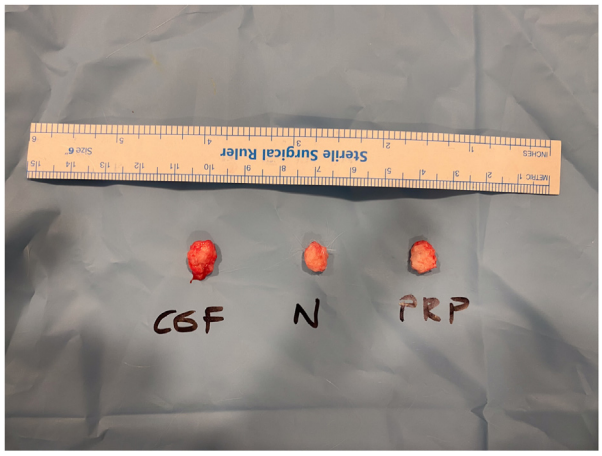

FIGURE 3. Cartilage grafts excised from the rabbit.

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HISTOPATHOLOGICAL EVALUATION

Cartilage tissue samples were fixed in 10% formaldehyde (pH 7.4) for 72 hours and passed through an ethanol series (50%, 70%, 90%, 96%, 100%) for 1 hour each. Then, it was kept in xylene for 30 minutes and blocked in hot paraffin. 5 μm thick sections were taken from the blocked tissues with a microtome (RM2235, Leica) and deparaffinized with xylene. It was then passed through an alcohol series (100%, 90%, 70%) and washed with distilled water. Sections taken were stained with Hematoxylin&Eosin for general histopathological examination and with Safranin-O&Fast Green to measure the amount of proteoglycan in the cartilage tissue matrix. Stained sections were passed through an alcohol series and xylene and covered with Entellan (1.07960, Sigma-Aldrich). The stained sections were examined with a light microscope (Carl Zeiss, Axio Observer) using a 20x/0.8 NA objective.[21] The histopathologist performing the histopathological evaluation was blind to the cartilages he examined.

DATA ANALYSIS

Statistical analysis was performed using GraphPad Prism version 8.0.0 software for Windows (GraphPad Software, San Diego, California, USA). All quantitative variables were evaluated using central location measures (ie, mean and median) and dispersion measures (ie, standard deviation [SD]).

The analysis of variance test was used to compare the quantitative data of the groups and to make comparisons between groups. A P value of $<.05$ was considered statistically significant.

Results

The final sample was composed of 14 rabbits and 42 specimens for analysis. In the ultra-diced graft cartilage group mean ± standard deviation histopathologic score was 11.93 ± 2.49. In the ultra-diced cartilage group mixed with PRP mean ± standard deviation histopathologic score was 8.78 ± 2.19. In the ultra-diced cartilage group mixed with CGF mean ± standard deviation histopathologic score was 6.85 ± 1.46. In the histopathological score comparison between the groups, statistically significant reductions were seen in the CGF-mixed ultra-diced cartilage ($P < .0001$) and PRP-mixed ultra-diced cartilage ($P < .0275$) groups compared to the ultra-diced cartilage group alone. There was no statistically significant difference in histopathological score between the CGF-mixed ultra-diced cartilage and PRP mixed ultra-diced cartilage groups ($P < .1605$) (Fig 4).

In the ultra-diced graft cartilage group mean ± standard deviation regenerative score was 6.21 ± 0.97. In the ultra-diced cartilage group mixed with PRP mean ± standard deviation regenerative score was 8.85 ± 1.70. In the ultra-diced cartilage group mixed with CGF mean ± standard deviation regenerative score was 12.07 ± 1.26. In the regenerative score comparison between the groups, statistically significant increases were seen in the CGF-mixed ultra-diced cartilage ($P < .0001$) and PRP-mixed ultra-diced cartilage ($P < .0159$) groups compared to the ultra-diced cartilage group alone. A statistically significant ($P < .0137$) regenerative score increase was seen in the CGF-mixed ultra-diced cartilage group compared to the PRP-mixed ultra-diced group (Fig 5).

In the ultra-diced cartilage group, wide spaces and sparse connective tissue stand out between the cartilage fragments. Loss of chondrocyte in the lacunae in the central and peripheral areas of the cartilage and fragmentation of the cartilage integrity as well as very rare blood vessel formation in the connective tissue around the cartilage tissue are observed (Fig 6).

In the ultra-diced cartilage group mixed with PRP, there is local tight connective tissue formation between the cartilage fragments, but there are also areas where the cartilage tissue is fragmented and not surrounded by connective tissue. In addition to increased blood vessel formation in the connective tissue, an

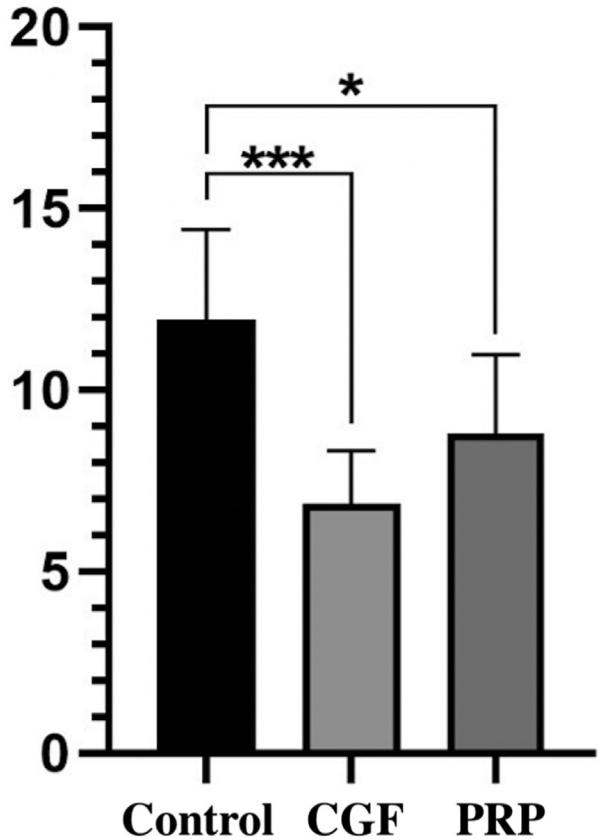

FIGURE 4. Histopathological score evaluation comparatively between groups. ***: $P < .0001$ and *: $P < .05$.

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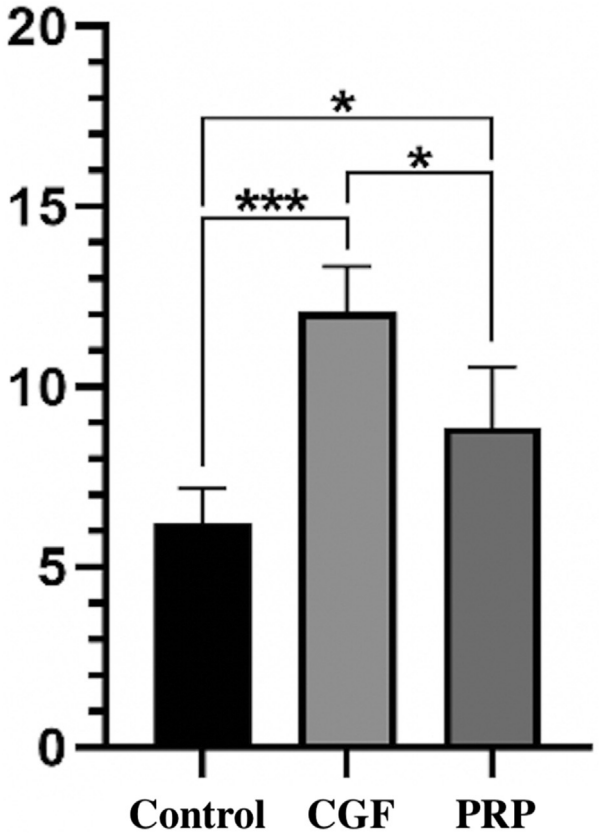

FIGURE 5. Regenerative score evaluation comparatively between groups. ***: $P < .0001$ and *: $P < .05$.

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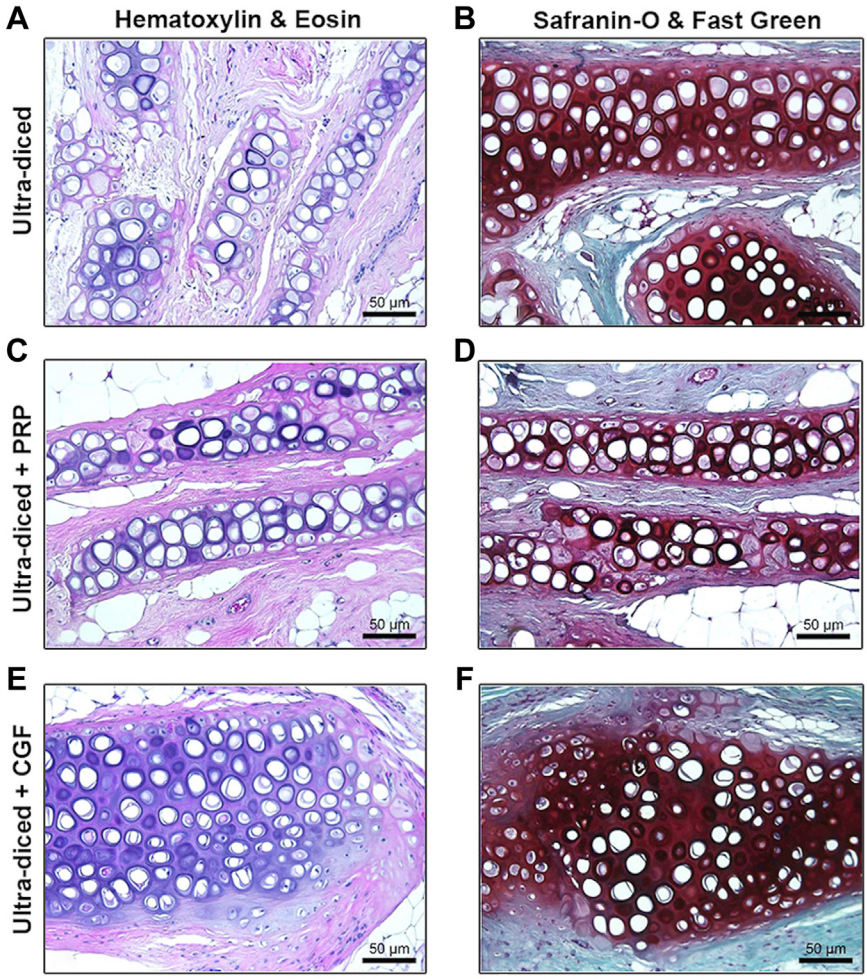

FIGURE 6. (*A*) Shredded areas of cartilage tissue and surrounding connective tissue are seen. (*B*) Dark (purple) stained territorial matrix around the lacunae in the cartilage tissue and the extra-territorial matrix around it and the connective tissue around the cartilage tissue (green). (*C*) Fragmented cartilage tissue peripherally located proliferative chondrocytes and blood vessels in connective tissue are seen. (*D*) Dark (purple) stained territorial matrix around the lacunae in the cartilage tissue and the extra-territorial matrix around it and the connective tissue around the cartilage tissue (green). (*E*) Hypertrophied cartilage tissue peripherally located proliferative chondrocytes and surrounding connective tissue is seen. (*F*) In the cartilage tissue, increased territorial matrix with dark (purple) staining around the lacunae and the extra-territorial matrix around it and the connective tissue around the cartilage tissue (green).

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increase in inflammation and calcified areas is also observed (Fig 6).

In the ultra-diced cartilage group mixed with CGF, the connective tissue tightly located around the cartilage fragments and increased blood vessel formation within this connective tissue is observed. However, chondrocytes in the lacunae in the cartilage tissue, proliferating chondrocytes located in the periphery of the cartilage tissue, and high proteoglycan content in the cartilage matrix are due to the increase in chondrocyte activities (Fig 6).

Discussion

The aim of rhinoplasty is to give the nose a natural and symmetrical appearance. However, sharp-edged and irregular nasal bones and cartilages may develop after nasal hump resection. Careful placement of a graft on the dorsum can prevent the skin from encountering irregular nasal structures, resulting in a smooth and symmetrical appearance. Some authors have suggested the use of autogenous soft tissue grafts such as temporal fascia or dermis to correct these irregularities. Soft tissue grafts are sufficient to hide dorsal irregularities, but their mass decreases over time.[3,5] Some authors have also suggested alloplastic materials such as Alloderm for this condition, but these materials have a risk of prolonged postoperative edema, high cost, and a short lifespan.[4] Therefore, autogenous cartilage is the ideal graft material for rhinoplasty because of its low graft rejection, infection, and minimal graft visibility.[6]

Diced cartilage 0.5-1 mm in size was first proven experimentally by Young in 1941, and then used clinically by Peer in 1943.[7,22] Diced cartilage used in rhinoplasty has less visibility and less chance of warping than large one-piece cartilage grafts. However, diced cartilage has two main problems, especially in thin-skinned patients: (1) a variable resorption rate and (2) the risk of distortion and migration. To solve these two problems, the diced cartilage has been wrapped with many materials to date.[20,23,24]

Since its introduction by Peer in 1943, there have been many studies investigating the usefulness of diced cartilage as a graft.[7] However, it was not until the 2000s that this graft gained popularity in rhinoplasty. In a 10-year study of 2365 patients, Erol found that diced cartilage wrapped with oxidized regenerated cellulose was suitable for strengthening the nasal dorsum and correcting dorsal irregularities.[8] Later, Yılmaz et al compared the viability of free diced cartilage with oxidized regenerated cellulose-wrapped diced cartilage in a rabbit model and found that oxidized regenerated cellulose reduced cartilage proliferation.[25] They showed that diced cartilage wrapped with oxidized regenerated cellulose was not metabolically active and had no regenerative potential. Oxidized regenerated cellulose is rarely used today because of severe foreign body reactions and its high resorption rate.[9,26]

The need to wrap the diced cartilage with fascia has emerged to strengthen the nasal dorsum and correct dorsal irregularities, especially in thin-skinned revision rhinoplasty surgeries. There are studies in which the long-term results of diced cartilage surrounded by temporal fascia have been satisfactory. In a study, Daniel and Calvert have shown that histopathologically, cartilage cells with normal regenerative potential and metabolically active and diced cartilage merge into a single cartilage mass.[9] They compared the clinical outcomes of free diced cartilage, oxidized regenerated cellulose, and diced cartilage wrapped with temporal fascia. They found satisfactory results in both free diced cartilage and fascia-wrapped diced cartilage. Later, Daniel et al popularized diced cartilage surrounded by temporal fascia to create a smooth and regular nasal ridge.[26]

Many blood products have also been tried for wrapping to increase the viability and survival rate of diced cartilage. The blood glue obtained by coagulation of venous blood has been reported as a scaffold for transporting and stabilizing the diced cartilage. However, Topkara et al showed in their study that venous blood glue did not significantly increase cartilage viability.[20] Studies with fibrin glue have shown that it increases cartilage growth and stabilization. Tasman et al used diced cartilage wrapped with fibrin glue, which is relatively costly compared to patients' own blood products for nasal augmentation. Histopathologically, cartilage viability and stability increased after a 15-month follow-up.[12]

Platelet concentrates contain growth factors that regulate the proliferation of cells through specific receptors. PRP is a first-generation platelet concentrate and is obtained by adding anticoagulants, calcium chloride and bovine thrombin to donor blood.[27] Manafi et al showed that diced cartilages supplemented with PRP achieved higher survival and regeneration capacity in a rabbit model.[11] Although PRP significantly increases cartilage viability because it is in liquid form, its function as a scaffold is limited. In our study, cartilage viability in the PRP group was significantly higher in terms of regenerative score and significantly lower in histopathological score compared to the control group.

CGF is obtained by centrifuging fresh venous blood at different speeds in a special centrifuge device. Compared to PRP, it has a three-dimensional fibrin structure that is denser, has better adhesion and regeneration capacity, and has a higher growth concentration. Topkara et al, in their study in rabbits, showed that mixing diced cartilage with CGF increased cartilage viability more than fascia.[20] Also, Bujia et al. In an in vitro study, showed that growth factors increase the proliferation of chondrocytes.[28] The authors highlight three advantages of CGF: (1) CGF contains cytokines that stimulate cell maturation and matrix production; (2) CGF is quick and easy to prepare; and (3) it is safe because it has no components other than autologous blood.[29] In our study, cartilage viability in the CGF group was found to be significantly higher in terms of regenerative score compared to the control and PRP groups, and significantly lower in terms of histopathological score compared to the control group.

Ultra-diced cartilage, which consists of cartilage fragments smaller than 0.2 mm, was first described by Taş. To obtain ultra-diced cartilage, the cartilage piece is first divided into small pieces of 2-3 mm then filled into an insulin syringe with a scalpel at the narrow end. After about 5 minutes of operation, the cartilages in the injector are cut into much smaller pieces and an ultra-diced cartilage is obtained. Electrostatic force holds these tiny particles together, and the ultra-diced cartilage forms a compact curved line during injection. In his study, Taş was able to demonstrate the viability of the ultra-diced cartilage in only 1 patient who underwent revision surgery.[18]

The effect of mixing the ultra-diced cartilage alone with PRP and CGF on viability was compared for the first time in this experimental study. In our study, according to histopathological findings, cartilage viability was found to be significantly lower in the groups mixed with CGF and PRP, compared to the control group, and the regeneration rate was found to be

significantly higher. When the CGF and PRP mixed ultra-diced cartilage groups were compared between themselves, there was no statistically significant difference in the resorption rate, while a statistically significant increase was found in the CGF mixed group in terms of regeneration rate.

The ideal wrapping method for ultra-diced or diced cartilage has not yet been determined. CGF is a good solution to the two main problems of cartilage grafts, namely wrapping and resorption. Therefore, it may be suitable as an autologous material for promoting grafts. In rhinoplasty operations, 10 ml of blood can be taken from the patient and the desired amount of CGF can be produced. Thus, a sufficient amount of ultra-diced cartilage mixed with CGF can be obtained for use on the dorsal, lateral nasal walls, and scroll area.

This study's limitations include the inability to measure the volume of the extracted grafts, the relatively small sample size, the lack of long-term follow-up to assess durability and potential complications, the fact that the semi-quantitative histopathological scoring system may lack precision and objectivity, and the inability to compare ultra-diced versus diced cartilage. The small sample size of only 14 rabbits, limits generalizability and statistical power. Animal studies with larger samples, longer duration, and comparing ultra-diced cartilage with diced cartilage are needed in the future. Additionally, the use of a rabbit model may not directly translate to human patients. There is a need for further research to validate findings, explore optimal concentrations and application techniques, and investigate long-term effects in human patients.

In conclusion, the search for an ideal autologous or nonautologous material for wrapping and stabilizing the diced cartilage continues today. Our study is the first to examine the ultra-diced cartilage in an experimental animal model. The ultra-diced cartilage undergoes some resorption when used alone. It has been shown that mixing the ultra-diced cartilage with CGF or PRP increases cartilage viability and reduces its resorption. It has been shown in our study that mixing the ultra-diced cartilage with CGF further increases cartilage viability and acts as a better structural scaffold compared to mixing it with PRP. However, these results need to be supported by long-term clinical studies. In addition, based on these results, the ultra-diced cartilage has the potential to be used as a dermal filler in the fascial region, type 1 thyroplasty, mastoid obliteration, patulous eustachian tube dysfunction, atrophic rhinitis, and empty nose syndrome.

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